Sleep Medicine
A Special Report

June 2021

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Help your patients living with narcolepsy

SEIZE THE DAY

With XYWAV—the first and only lower-sodium oxybate FDA approved for treating cataplexy or EDS* in patients ages 7 years and older with narcolepsy.[1-3]

*Excessive daytime sleepiness.

xywav™

(calcium, magnesium, potassium, and sodium oxybates) oral solution

AVAILABLE FOR PRESCRIPTION!

Consider XYWAV

Whether a patient is taking XYREM® (sodium oxybate) oral solution now or is new to oxybate treatment.

Learn more at XywavHCP.com

92% less sodium than sodium oxybate[3]

XYWAV contains the same active moiety at the same concentration as XYREM® (sodium oxybate) oral solution.[1,4] Both contain 0.413 g/mL of oxybate in solution.[1,4]

Visit **XywavHCP.com** to sign up for information and learn more about how to start or transition appropriate patients.

INDICATIONS AND USAGE

XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL total salts (equivalent to 0.413 g/mL of oxybate) is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

Important Safety Information

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- **Central Nervous System Depression**

XYWAV is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with XYWAV at recommended doses. Many patients who received XYWAV during clinical trials in narcolepsy were receiving CNS stimulants.

- **Abuse and Misuse**

The active moiety of XYWAV is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death.

Because of the risks of CNS depression and abuse and misuse, XYWAV is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Xywav and Xyrem REMS.

Please see additional Important Safety Information on the following pages and Brief Summary of full Prescribing Information, including BOXED Warning.

xywav™

(calcium, magnesium, potassium, and sodium oxybates) oral solution

Important Safety Information (continued)

Contraindications

XYWAV is contraindicated in combination with sedative hypnotics or alcohol and in patients with succinic semialdehyde dehydrogenase deficiency.

Warnings and Precautions

- CNS Depression: Use caution when considering the concurrent use with other CNS depressants. If concurrent use is required, consider dose reduction or discontinuation of one or more CNS depressants (including XYWAV). Consider interrupting XYWAV treatment if short-term opioid use is required. After first initiating treatment and until certain that XYWAV does not affect them adversely, caution patients against hazardous activities requiring complete mental alertness or motor coordination such as operating hazardous machinery, including automobiles or airplanes. Also caution patients against these hazardous activities for at least 6 hours after taking XYWAV. Patients should be queried about CNS depression-related events upon initiation of XYWAV therapy and periodically thereafter.
- Abuse and Misuse: XYWAV is a Schedule III controlled substance. The rapid onset of sedation, coupled with the amnestic features of GHB particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (eg, assault victim).
- Respiratory Depression and Sleep-Disordered Breathing: XYWAV may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses of oxybate and with illicit use of GHB, life-threatening respiratory depression has been reported. Increased apnea and reduced oxygenation may occur with XYWAV administration in adult and pediatric patients. A significant increase in the number of central apneas and clinically significant oxygen desaturation may occur in patients with obstructive sleep apnea treated with XYWAV. Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy, and among patients with narcolepsy.
- Depression and Suicidality: In a randomized-withdrawal clinical trial in adult patients with narcolepsy (n=201), depression and depressed mood were reported in patients treated with XYWAV. In most cases, no change in XYWAV treatment was required. In clinical trials of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy (n=781), depression was reported by 7% of Xyrem-treated patients, with four patients (<1%) discontinuing because of depression. In the pediatric clinical trial with Xyrem in patients with narcolepsy (n=104), one patient experienced suicidal ideation, and two patients reported depression while taking XYREM. Monitor patients for the emergence of increased depressive symptoms and/or suicidality while taking XYWAV, which require careful and immediate evaluation.
- Other Behavioral or Psychiatric Adverse Reactions: Monitor patients for impaired motor/cognitive function or the emergence of or increase in anxiety and/or confusion. The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking XYWAV should be carefully monitored.
- Parasomnias: In a randomized-withdrawal clinical trial, parasomnias, including sleepwalking were reported in adult patients treated with XYWAV. Parasomnias, including sleepwalking, also have been reported in a pediatric clinical trial with sodium oxybate (same active moiety as XYWAV) and in postmarketing experience with sodium oxybate. Episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

Most Common Adverse Reactions

In the adult clinical trial, in patients with narcolepsy, the most common adverse reactions (incidence ≥5% of XYWAV-treated patients) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.

In the pediatric clinical trial with Xyrem (same active moiety as XYWAV) in patients 7 years of age and older with narcolepsy, the most common adverse reactions (≥5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%). The safety profile in pediatric patients with XYWAV is expected to be similar to that of adult patients treated with XYWAV and to that of pediatric patients treated with Xyrem.

Please see additional Important Safety Information on previous page and Brief Summary of full Prescribing Information, including BOXED Warning, on following pages.

References: 1. XYWAV™ (calcium, magnesium, potassium, and sodium oxybates). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** Thorpy MJ. Recently approved and upcoming treatments for narcolepsy. *CNS Drugs.* 2020;34(1):9-27. **3.** Bogan RK, Thorpy MJ, Dauvilliers Y, et al. Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy. *Sleep.* Published online October 14, 2020. doi.org/10.1093/sleep/zsaa206. **4.** XYREM® (sodium oxybate). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.

xywav™

(calcium, magnesium, potassium, and sodium oxybates) oral solution

Jazz Pharmaceuticals®

XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII

BRIEF SUMMARY OF PRESCRIBING INFORMATION: Consult the full Prescribing Information for complete product information.

Initial U.S. Approval: 2002

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- **Central Nervous System Depression**
  XYWAV is a CNS depressant, and respiratory depression can occur with XYWAV use *[see Warnings and Precautions (5.1)(5.4)]. Many patients who received XYWAV during clinical trials in narcolepsy were receiving central nervous system stimulants [see Clinical Trials (14)].*
- **Abuse and Misuse**
  The active moiety of XYWAV is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death *[see Warnings and Precautions (5.2)]*.
  XYWAV is available only through a restricted program called the XYWAV and XYREM REMS *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

XYWAV is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

4 CONTRAINDICATIONS

XYWAV is contraindicated for use in:

- combination with sedative hypnotics *[see Warnings and Precautions (5.1)]*.
- combination with alcohol *[see Warnings and Precautions (5.1)]*.
- patients with succinic semialdehyde dehydrogenase deficiency *[see Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

XYWAV is a central nervous system (CNS) depressant. Clinically significant respiratory depression and obtundation has occurred in adult patients taking sodium oxybate (same active moiety as XYWAV) at recommended doses in clinical trials and may occur in patients treated with XYWAV at recommended doses. XYWAV is contraindicated in combination with alcohol and sedative hypnotics. The concurrent use of XYWAV with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.

If use of these CNS depressants in combination with XYWAV is required, dose reduction or discontinuation of one or more CNS depressants (including XYWAV) should be considered. In addition, if short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYWAV should be considered.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that XYWAV does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking XYWAV. Patients should be queried about CNS depression-related events upon initiation of XYWAV therapy and periodically thereafter.

XYWAV is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)]*.

5.2 Abuse and Misuse

XYWAV is a Schedule III controlled substance. The active moiety of XYWAV is oxybate, also known as gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been reported, healthcare providers should carefully evaluate patients for a history of drug abuse and follow them closely, particularly for signs of misuse or abuse of GHB (including but not limited to increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) *[see Drug Abuse and Dependence (9.2)]*. If abuse is suspected, treatment with XYWAV should be discontinued.

XYWAV is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)]*.

5.3 XYWAV and XYREM REMS

XYWAV is available only through a restricted distribution program called the XYWAV and XYREM REMS because of the risks of central nervous system depression and abuse and misuse *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the XYWAV and XYREM REMS include the following:

- Healthcare Providers who prescribe XYWAV are specially certified
- XYWAV will be dispensed only by the central pharmacy that is specially certified
- XYWAV will be dispensed and shipped only to patients who are enrolled in the XYWAV and XYREM REMS with documentation of safe use.

Further information is available at www.XYWAVXYREMREMS.com or 1-866-997-3688.

5.4 Respiratory Depression and Sleep-Disordered Breathing

XYWAV may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses of oxybate and with illicit use of GHB, life-threatening respiratory depression has been reported *[see Overdosage (10)]*.

Increased apnea and reduced oxygenation may occur with XYWAV administration in adult and pediatric patients. A significant increase in the number of central apneas and clinically significant oxygen desaturation may occur in patients with obstructive sleep apnea treated with XYWAV.

In a study assessing the respiratory-depressant effects of Xyrem (same active moiety as XYWAV) at doses up to 9 g per night in 21 adult patients with narcolepsy, no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of the four patients with preexisting moderate-to-severe sleep apnea had significant worsening of the apnea/hypopnea index during treatment.

In a study assessing the effects of Xyrem 9 g per night in 50 adult patients with obstructive sleep apnea, Xyrem did not increase the severity of sleep-disordered breathing and did not adversely affect the average duration and severity of oxygen desaturation overall. However, there was a significant increase in the number of central apneas in patients taking Xyrem, and clinically significant oxygen desaturation (≤55%) was measured in three patients (6%) after Xyrem administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation.

During polysomnographic evaluation (PSG), central sleep apnea and oxygen desaturation were observed in pediatric patients with narcolepsy treated with Xyrem.

Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with sodium oxybate administration in adult and pediatric patients.

In clinical trials of Xyrem in 128 adult patients with narcolepsy, two patients had profound CNS depression, which resolved after supportive respiratory intervention. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing PSG measures in adult patients with narcolepsy, 40 of 477 patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function, as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night.

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy, and among patients with narcolepsy.

5.5 Depression and Suicidality

Depression, and suicidal ideation and behavior can occur in patients treated with XYWAV.

In Study 1, depression and depressed mood were reported in 3% and 4%, respectively, of patients treated with XYWAV. Two patients (1%) discontinued XYWAV because of depression, but in most cases, no change in XYWAV treatment was required.

In clinical trials of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy (n=781), there were two suicides and two attempted suicides in patients treated with Xyrem, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used Xyrem in conjunction with other drugs. Xyrem was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 patients treated with Xyrem, with four patients (<1%) discontinuing because of depression. In most cases, no change in Xyrem treatment was required. In a clinical trial with Xyrem in pediatric patients with narcolepsy (n=104), one patient experienced suicidal ideation and two patients reported depression while taking Xyrem.

The emergence of depression in patients treated with XYWAV requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking XYWAV.

5.6 Other Behavioral or Psychiatric Adverse Reactions

Other behavioral and psychiatric adverse reactions can occur in patients taking XYWAV. In Study 1, confusion occurred in 1% of patients treated with XYWAV and anxiety occurred in 5% of patients treated with XYWAV. One patient experienced visual hallucinations and confusion after ingesting approximately 9 grams of XYWAV. Other neuropsychiatric reactions reported in clinical trials of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy and in the postmarketing setting included hallucinations, paranoia, psychosis, aggression, and agitation.

In a pediatric clinical trial with Xyrem in patients with narcolepsy, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety, were reported while taking Xyrem.

The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking XYWAV should be carefully monitored.

5.7 Parasomnias

Parasomnias can occur in patients taking XYWAV.

In Study 1, parasomnias, including sleepwalking, were reported in 6% of patients treated with XYWAV. In a clinical trial of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy, five instances of sleepwalking with potential injury or significant injury were reported. Parasomnias, including sleepwalking, also have been reported in a pediatric clinical trial with sodium oxybate and in postmarketing experience with sodium oxybate.

Episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions appear in other sections of the labeling:

- CNS depression *[see Warnings and Precautions (5.1)]*
- Abuse and Misuse *[see Warnings and Precautions (5.2)]*
- Respiratory Depression and Sleep-Disordered Breathing *[see Warnings and Precautions (5.4)]*
- Depression and Suicidality *[see Warnings and Precautions (5.5)]*
- Other Behavioral or Psychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Parasomnias *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adult Patients

The safety of XYWAV was evaluated in a 16-week double-blind placebo-controlled randomized-withdrawal study in patients with narcolepsy with cataplexy (Study 1), which was followed by an open-label extension phase lasting 24 weeks *[see Clinical Studies (14.1)]*. Study 1 included an open-label titration period (OL OTTP), a stable-dose period (SDP), and a double-blind, placebo-controlled, randomized-withdrawal period (DB RWP). A total of 201 patients, ages 18 to 70 years, received XYWAV at individually titrated doses for 14 weeks, followed by randomization to XYWAV or matching placebo for 2 weeks of treatment. The mean exposure to XYWAV during this study, including titration, the randomized withdrawal period, and the open-label extension, was 151 days. In patients who remained on treatment, adverse reactions tended to occur early and diminish over time.

Adverse Reactions Leading to Treatment Discontinuation

In Study 1, 9 of 201 patients (4%) reported adverse reactions that led to withdrawal from the study (anxiety, decreased appetite, depressed mood, depression, fatigue, headache, irritability, nausea, pain in extremity, parasomnia, somnolence, and vomiting). The most common adverse reaction leading to discontinuation was nausea (1.5%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

Commonly Observed Adverse Reactions

The most common adverse reactions in Study 1 (incidence ≥ 5% of XYWAV-treated patients) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or Greater:

Table 1 lists adverse reactions observed in the open-label titration and stable dose periods of Study 1 that occurred at a frequency of 2% or greater in adult patients treated with XYWAV.

Table 1:

Adverse Reactions Occurring in ≥2% of Adult Patients Treated with XYWAV in the Open-Label Titration and Stable Dose Periods in Study 1*

Adverse Reaction	Open-Label Titration Period + Stable Dose Period (14 weeks) (N=201) %
Headache	20
Nausea	13
Dizziness	10
Decreased appetite	8
Parasomnia†	6
Diarrhea	6
Hyperhidrosis‡	6
Anxiety§	5
Vomiting	5
Fatigue¶	4
Dry mouth	4
Depressed mood	4
Enuresis	4
Irritability	3
Paresthesia	3
Depression	3
Tremor	3
Somnolence	2
Muscle spasms	2

*Adverse reactions related to XYWAV were reported less frequently, as an overall incidence, in patients on Xyrem at study entry than in Xyrem-naïve patients.

†Includes abnormal dreams, abnormal sleep-related event, rapid eye movements sleep abnormal, sleep paralysis, sleep talking, sleep terror, sleep-related eating disorder, somnambulism

‡Includes hyperhidrosis and night sweats

§Includes anxiety, agitation, panic attack, tension

¶Includes fatigue and asthenia

Adverse Reactions Observed in Clinical Studies with Xyrem (≥2%), but not in Study 1, and Which May Be Relevant for XYWAV

Pain, feeling drunk, pain in extremity, cataplexy, disturbance in attention, sleep paralysis, and disorientation.

Pediatric Patients (7 Years of Age and Older)

In the pediatric clinical trial with Xyrem (same active moiety as XYWAV), 104 patients aged 7 to 17 years (37 patients aged 7 to 11 years; 67 patients aged 12 to 17 years) with narcolepsy received Xyrem for up to one year *[see Clinical Studies (14.2)]*. This study included an open-label safety continuation period in which eligible patients received Xyrem for up to an additional 2 years. The median and maximum exposure across the entire study were 371 and 987 days, respectively.

Adverse Reactions Leading to Treatment Discontinuation

In the pediatric clinical trial with Xyrem, 7 of 104 patients reported adverse reactions that led to withdrawal from the study (hallucination, tactile; suicidal ideation; weight decreased; sleep apnea syndrome; affect lability; anger, anxiety, depression; and headache).

Adverse Reactions in the Xyrem Pediatric Clinical Trial

The most common adverse reactions (≥5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%).

Additional information regarding safety in pediatric patients appears in the following sections:

- Respiratory Depression and Sleep-Disordered Breathing *[see Warnings and Precautions (5.4)]*
- Depression and Suicidality *[see Warnings and Precautions (5.5)]*
- Other Behavioral or Psychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Parasomnias *[see Warnings and Precautions (5.7)]*

The overall adverse reaction profile of Xyrem in the pediatric clinical trial was similar to that seen in the adult clinical trial program. The safety profile in pediatric patients with XYWAV is expected to be similar to that of adult patients treated with XYWAV and to that of pediatric patients treated with Xyrem.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sodium oxybate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Arthralgia, fall*, fluid retention, hangover, hypersensitivity, hypertension, memory impairment, nocturia, and vision blurred.

*The sudden onset of sleep in patients taking sodium oxybate, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization.

7 DRUG INTERACTIONS

7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

XYWAV is contraindicated for use in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of XYWAV *[see Warnings and Precautions (5.1)]*.

7.2 Divalproex Sodium

Concomitant use of sodium oxybate with divalproex sodium results in an increase in systemic exposure to GHB, which was shown to cause a greater impairment on some tests of attention and working memory in a clinical study *[see Clinical Pharmacology (12.3)]*. A similar increase in exposure is expected with concomitant use of XYWAV and divalproex sodium; therefore, an initial dose reduction of XYWAV is recommended when used concomitantly with divalproex sodium *[see Dosage and Administration (2.6)]*. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of XYWAV and divalproex sodium is warranted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of XYWAV or sodium oxybate in pregnant women. Oral administration of sodium oxybate to pregnant rats (0, 150, 350, or 1,000 mg/kg/day) or rabbits (0, 300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity; however, oral administration to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and growth, at a clinically relevant dose *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Labor or Delivery

XYWAV has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid, and gamma-hydroxybutyrate (GHB) has been detected in newborns at delivery after intravenous administration of GHB to mothers. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

Data

Animal Data

Oral administration of sodium oxybate to pregnant rats (0, 150, 350, or 1,000 mg/kg/day) or rabbits (0, 300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses of sodium oxybate tested in rats and rabbits were approximately 1 and 3 times, respectively, the maximum recommended human dose (MRHD) of 9 g per night on a body surface area (mg/m^2) basis.

Additionally, oral administration of sodium oxybate (0, 150, 350, or 1,000 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and body weight gain at the highest dose tested. The no-effect dose for pre- and post-natal developmental toxicity in rats is less than the MRHD on a mg/m^2 basis.

8.2 Lactation

Risk Summary

GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XYWAV and any potential adverse effects on the breastfed infant from XYWAV or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of XYWAV for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy have been established. XYWAV has not been studied in a pediatric clinical trial. Use of XYWAV in pediatric patients 7 years of age and older with narcolepsy is supported by evidence from an adequate and well-controlled study of sodium oxybate in pediatric patients 7 to 17 years of age, a study in adults showing a treatment effect of XYWAV similar to that observed with sodium oxybate, pharmacokinetic data of sodium oxybate from adult and pediatric patients, and pharmacokinetic data of XYWAV from healthy adult volunteers *[see Adverse Reactions (6.1) and Clinical Studies (14.1, 14.2)]*.

In the pediatric clinical trial with sodium oxybate administration in patients with narcolepsy, serious adverse reactions of central sleep apnea and oxygen desaturation documented by polysomnography evaluation; depression; suicidal ideation; neuropsychiatric reactions including acute psychosis, confusion, and anxiety; and parasomnias, including sleepwalking, have been reported *[see Warnings and Precautions (5.4, 5.5, 5.6, 5.7) and Adverse Reactions (6.1)]*.

Safety and effectiveness of XYWAV in pediatric patients below the age of 7 years have not been established.

Juvenile Animal Toxicity Data

In a study in which sodium oxybate (0, 100, 300, or 900 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 21 through 90), mortality was observed at the two highest doses tested. Deaths occurred during the first week of dosing and were associated with clinical signs (including decreased activity and respiratory rate) consistent with the pharmacological effects of the drug. Reduced body weight gain in males and females and delayed sexual maturation in males were observed at the highest dose tested. The no-effect dose for adverse effects in juvenile rats is associated with plasma exposures (AUC) less than that at the maximum recommended human dose (9 g/night).

8.5 Geriatric Use

Clinical studies of XYWAV or Xyrem in patients with narcolepsy did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

In clinical studies of sodium oxybate in another population, 39 (5%) of 874 patients were 65 years or older. Discontinuations of treatment due to adverse reactions were increased in the elderly compared to younger adults (21% vs. 19%). Frequency of headaches was markedly increased in the elderly (39% vs. 19%). The most common adverse reactions were similar in both age categories. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Because of an increase in exposure to XYWAV, the starting dose should be reduced by half in patients with hepatic impairment *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

XYWAV is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of XYWAV could lead to penalties assessed under the higher Schedule I controls.

9.2 Abuse

The active moiety of XYWAV, oxybate, produces dose-dependent central nervous system effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse.

Drug abuse is the intentional non-therapeutic use of a drug product or substance, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug misuse and abuse may occur with or without progression to addiction. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalities with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy). Dispose of XYWAV according to state and federal regulations. It is safe to dispose of XYWAV down the sanitary sewer.

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of XYWAV have not been systematically evaluated in controlled clinical trials. In the clinical trial experience with Xyrem in narcolepsy/cataplexy patients at recommended doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time. In the XYWAV clinical trial in adult narcolepsy/cataplexy patients at recommended doses, one patient reported insomnia following abrupt discontinuation of XYWAV.

Tolerance

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to XYWAV has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended XYWAV dosage regimen. Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of XYWAV in the treatment of alcohol withdrawal have not been established.

10 OVERDOSAGE

10.1 Human Experience

Information regarding overdose with XYWAV is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances the co-ingestion of other drugs and alcohol was common, and may have influenced the presentation and severity of clinical manifestations of overdose.

In adult clinical trials with Xyrem (same active moiety as XYWAV), two cases of overdose were reported. In the first case, an estimated dose of 150 g, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of Xyrem and numerous other drugs. No cases of overdose (greater than 9 g) with XYWAV were reported in the XYWAV clinical trial.

10.2 Signs and Symptoms

Information about signs and symptoms associated with overdosage with XYWAV derives from reports of illicit use of GHB. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills have been observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported. Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

10.3 Recommended Treatment of Overdose

General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to atropine intravenous administration. No reversal of the central depressant effects of XYWAV can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB overdose. However, due to the rapid metabolism of oxybate, these measures are not warranted.

10.4 Poison Control Center

As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center (1-800-222-1222) for current treatment recommendations.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Central Nervous System Depression

Inform patients and/or caregivers that XYWAV can cause central nervous system depression, including respiratory depression, hypotension, profound sedation, syncope, and death. Instruct patients not to engage in activities requiring mental alertness or motor coordination, including operating hazardous machinery, for at least 6 hours after taking XYWAV. Instruct patients and/or their caregivers to inform their healthcare providers of all the medications they take *[see Warnings and Precautions (5.1)]*.

Abuse and Misuse

Inform patients and/or caregivers that the active ingredient of XYWAV is gamma-hydroxybutyrate (GHB), which is associated with serious adverse reactions with illicit use and abuse *[see Warnings and Precautions (5.2)]*.

XYWAV and XYREM REMS

XYWAV is available only through a restricted program called the XYWAV and XYREM REMS *[see Warnings and Precautions (5.3)]*. Inform the patient and/or caregiver of the following notable requirements:

- XYWAV is dispensed only by the central pharmacy
- XYWAV will be dispensed and shipped only to patients enrolled in the XYWAV and XYREM REMS

XYWAV is available only from the central pharmacy participating in the program. Therefore, provide patients and/or caregivers with the telephone number and website for information on how to obtain the product.

Alcohol or Sedative Hypnotics

Advise patients and/or caregivers that alcohol and other sedative hypnotics should not be taken with XYWAV *[see Contraindications (4)]*.

Sedation

Inform patients and/or caregivers that the patient is likely to fall asleep quickly after taking XYWAV (often within 5 and usually within 15 minutes), but the time it takes to fall asleep can vary from night to night. The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization *[see Adverse Reactions (6.2)]*. Instruct patients and/or caregivers that the patient should remain in bed following ingestion of each dose. Instruct patients and/or caregivers that the patient should not take a subsequent nightly dose until at least 2.5 to 4 hours after the previous dose *[see Dosage and Administration (2.3)]*.

Administration Instructions

Inform patients and/or caregivers that the total nightly dosage of XYWAV is divided into two doses and that the first nightly dose of XYWAV should be taken at least 2 hours after eating.

Respiratory Depression and Sleep-Disordered Breathing

Inform patients that XYWAV may impair respiratory drive, especially in patients with compromised respiratory function, and may cause apnea *[see Warnings and Precautions (5.4)]*.

Depression and Suicidality

Instruct patients and/or caregivers to contact a healthcare provider immediately if the patient develops depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or suicidal ideation *[see Warnings and Precautions (5.5)]*.

Other Behavioral or Psychiatric Adverse Reactions

Inform patients and/or caregivers that XYWAV can cause behavioral or psychiatric adverse reactions, including confusion, anxiety, and psychosis. Instruct them to notify their healthcare provider if any of these types of symptoms occur *[see Warnings and Precautions (5.6)]*.

Sleepwalking

Instruct patients and/or caregivers that XYWAV has been associated with sleepwalking and other behaviors during sleep, and to contact their healthcare provider if this occurs *[see Warnings and Precautions (5.7)]*.

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Sleep problems likely to become more common because of pandemic

BY RUTH M. BENCA, MD, PHD

In the midst of the COVID-19 pandemic, we also face a dramatic increase in psychiatric disorders and behavioral issues that it has triggered, including insomnia, mood and anxiety disorders, and suicide. While most of the studies reported in this issue were not performed during the pandemic, they all describe issues that are likely to become even more common both during the pandemic as well as in its aftermath.

Dr. Benca

Two of the reports describe addictive behaviors and their sequelae that are particularly common in adolescents: excessive use of smartphones (see page 10) and vaping e-cigarettes (see page 13). Both are associated with sleep deprivation and delayed sleep patterns. Smartphone use often increases at night and exposure to screen lighting may promote a phase shift, whereas nicotine from e-cigarettes, particularly when used in the evening, can interfere with sleep through its stimulant properties.

Younger generations who have grown up with smartphones have become highly dependent on them for many activities in their daily lives. The social isolation resulting from the pandemic lockdown has made smartphones the predominant form of communication and has only heightened youths' dependency on them.

"Nomophobia," or the fear and anxiety of being without access to a smartphone, describes the psychological effects of loss of a major means of social interaction and, as reported in the study by Peszka, results in sleep disturbance. Similarly, e-cigarette use has been increasing dramatically in adolescents and young adults. The study by Kianarsi, which surveyed almost 19,000 young adults, found that greater use of e-cigarettes was associated with a significantly greater degree of sleep deprivation. Both smartphones and e-cigarettes have also been associated with increased risk of anxiety and depression in those who use them most frequently.

Pregnant women and the elderly are particularly at risk for sleep problems and additional health issues secondary to sleep problems. In pregnant women, economic concerns and fears about contracting the virus by mother and baby have led to increased rates of COVID-induced insomnia, anxiety, and depression. The article by Cohen describes Virtual Rounds at the Center for Women's Health at Massachusetts General Hospital in Boston, which provides a forum to discuss cases and treatment approaches for pregnant and postpartum women. (See page 17.) The prospective study by Robbins and colleagues demonstrated that those aged 65 years and older who report sleeping less than 5 hours per night were more likely to develop Alzheimer's disease or die over the next 5 years. (See page 25.) Health risks related to insufficient sleep in the elderly could be exacerbated during the pandemic, because sleep loss is associated with increased risk of infections as well as decreased responsivity to immunization.

Finally, the study by Skobic and colleagues reports that, in a group of subjects who had experienced job loss, those who had insomnia had increased experiences of subsequent stress, compared with those who did not have insomnia following job loss. This suggests that people who tend to react to stress by developing insomnia are more likely to experience continued stress, setting up a vicious cycle between stress and insomnia. This is particularly concerning given the dramatic increase in multiple, severe stressors caused by the pandemic. (See page 15.)

In summary, the reports in this issue describe at-risk groups for in-

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Sleep Medicine A Special Report

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Sleep Medicine is a special report to Clinical Psychiatry News, Family Practice News, Internal Medicine News, Pediatric News, and Neurology Reviews, independent newspapers that provide the practicing physician with timely and relevant news and commentary about clinical developments in their field and about the impact of health care policy on the specialty and the physician's practice.

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Dementia's link to sleep-related conditions, problems with daylight saving time addressed

BY KRISHNA M. SUNDAR, MD

The impact of a number of sleep-related conditions on the occurrence of dementia is one of the most topical subjects addressed in this publication.

The incidence of dementia is an increasing problem worldwide as people continue to live longer. Inside is a noteworthy article on the relationship between adherence to therapy for obstructive sleep apnea (OSA) with continuous positive airway pressure and the risk of incident dementia. (See page 22.) You can also read about dementia risk in older adults being magnified with sleep medication use. (See page 25.)

Dr. Sundar

Despite the changes in sleep and work schedules caused by COVID, the biannual change of clocks to accommodate daylight saving time continues to have an impact on health. One of the articles draws attention to this problem by discussing the American Academy of Sleep Medicine's recent call to eliminate daylight saving time in a statement. (See page 14.)

Other articles continue to highlight the variation of OSA expression with race and increasing burden of disease stemming from comorbid insomnia in frequently encountered chronic diseases such as chronic obstructive pulmonary disorder.

Dr. Sundar is currently the medical director of the Sleep-Wake Center and clinical professor in the department of medicine, University of Utah, Salt Lake City. He is board certified in sleep medicine, pulmonary disease, critical care medicine, and internal medicine.

Following his medical training in Delhi University and postgraduate training in PGIMER, Chandigarh, India, Dr. Sundar completed his residency in internal medicine at St. Luke's-Roosevelt Hospital, Columbia University, New York, and a fellowship in pulmonary, critical care medicine, and sleep medicine at the University of Utah.

He is a full-time associate professor at the University of Utah, where he has expanded the school's sleep program in terms of its clinical, research, and teaching opportunities. He also directs a multidisciplinary chronic cough clinic at the Voice Disorders Center, University of Utah.

Dr. Sundar has authored more than 50 peer-reviewed publications in pulmonary, critical care, and sleep medicine. He is actively involved in clinical and translational research in a number of areas, including the basis of sleep-disordered breathing, chronic cough, patterns of chronic hypoxia, and outcomes from sleep apnea. He has mentored a number of residents and fellows and has been recognized for teaching and clinical excellence. He serves on the editorial advisory board of CHEST Physician and has lectured on a wide range of topics at international conferences.

Dr. Sundar serves on the advisory board to Merck. He is a cofounder of Hypnoscure, created through the University of Utah Technology Commercialization Office, aimed at software creation for population management of sleep disorders.

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somnia, behaviors that contribute to sleep disturbance, and health risks associated with sleep disturbance. All of the reports are particularly relevant during the COVID-19 pandemic, as insomnia and psychiatric illnesses have increased dramatically, largely related to the multitude of pandemic-related stressors. They highlight the importance of assessing and treating sleep problems in our patients, now more than ever.

Dr. Benca is professor and chair of the department of psychiatry and human behavior at the University of California, Irvine. She received her bachelor of arts degree from Harvard University and her MD and PhD degrees from the University of Chicago. She has been a faculty member at the University of Chicago and the University of Wisconsin–Madison, where she was associate chair of the psychiatry department and director of the UW Center for Sleep Medicine and Sleep Research.

Dr. Benca moved to UC Irvine in 2016, where she has established a sleep medicine center, which provides clinical care for sleep disorders and promotes translational research.

Her research focuses on the interface between sleep and psychiatric disorders across the life span, and the role of sleep and sleep disorders on Alzheimer's disease. She has served as principal investigator for studies funded by agencies, including the National Institutes of Health and the Department of Defense. Her work has spanned basic research in animal models to clinical research and clinical trials. Dr. Benca has authored over 150 articles, reviews, and book chapters. She currently is editor-in-chief of Current Sleep Medicine Reports and insomnia section editor for UpToDate.

Dr. Benca has served as a consultant to Eisai, Idorsia Pharmaceuticals, Genomind, Jazz Pharmaceuticals, Merck, and Sunovion.

‘No mobile phone’ phobia tied to sleep problems in college students

BY MEGAN BROOKS

“Nomophobia” – the fear of being without a mobile phone or out of mobile phone contact – is extremely prevalent among college students and is associated with poor sleep habits and fatigue. In a study of more than 300 college students, nearly 9 in 10 (89%) were classified as having moderate to severe nomophobia. Greater levels of nomophobia were significantly linked to daytime sleepiness and more behaviors associated with poor sleep hygiene.

“My undergraduate research team came up with the idea for this study,” said study investigator Jennifer Peszka, PhD, professor of psychology at Hendrix College, Conway, Ark. She explained that her students had been looking at the impact of technology use in the 2 hours before bed, and hypothesized that “cell phone addiction” might play a role in sleep problems.

Incidentally, “that group of students were all pretty high on nomophobia themselves so they were really interested in the outcome,” Dr. Peszka said.

The study findings were presented at the virtual annual meeting of the Associated Professional Sleep Societies.

A likely suspect

The study involved 327 undergraduates (mean age, 19.7

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Peter Cade/Stone/Getty Images

Commentary by Dr. Benca

Use of smartphones has become almost ubiquitous in modern society. These devices are used for an ever-increasing range of activities, including social interaction, entertainment, learning, shopping, and so on, raising the question of whether distress upon disconnection from such a vital communication tool should be considered a psychological disorder or a predictable response to sudden social isolation!

Nomophobia, or fear of being without a mobile phone, is understandably increased when there is extreme reliance on its use. The study by Peszka and colleagues found a high prevalence of moderate to severe nomophobia (89%) in a survey of undergraduate college students; several other studies have similarly found adolescents and young adults to have reported rates of at least 80%. Factors that are consistently associated with higher levels of nomophobia include younger age and more hours of daily phone use. This suggests again that greater reliance on mobile phones as a primary route of communication results in more severe distress upon the threat of losing them.

Not surprisingly, excessive phone use and nomophobia are strongly related to sleep problems. Excessive use of smartphones is associated with insomnia, reduced sleep quality, and sleep loss. Teenagers and young adults who already have a tendency to be “night owls” often use smartphones late into the night. The results of the study reported here further support these associations, with increased use of the phone during sleep time and more daytime sleepiness associated with greater nomophobia. More severe nomophobia occurs in those with greater anxiety or depression, both of which in turn are strongly associated with disturbed sleep; in the current study, decreased motivation – a symptom of depression – was also associated with nomophobia.

Other potential health risks have been linked with nomophobia. Increased rates of both prohibited (that is, using a cell phone in a restricted area) and dangerous (that is, using a cell phone while driving) use of cell phones have been reported in younger individuals, with increased hours of daily phone use, increased nomophobia, and in males, higher concerns for more accidents and injuries.

Clearly, extreme nomophobia might identify individuals with psychological characteristics that can put them at risk for other disorders. Further work is needed to identify risk factors for nomophobia, particularly in young people. How does living a significant portion of waking life virtually through cell phones affect psychological development during the critical period of adolescence? These issues are further intensified during the COVID-19 pandemic, which has led to severe social isolation for young people due to school closures and elimination of sports and social activities.

Smartphone 'addiction' tied to poor sleep in young adults

BY MEGAN BROOKS

Smartphone "addiction" may explain poor sleep quality in a significant proportion of young adults, new research suggests.

Investigators found that almost 40% of adults aged 18-30 years who self-reported excessive smartphone use also reported poor sleep.

"Our study provides further support to the growing body of evidence that smartphone addiction has a deleterious impact on sleep," wrote the researchers.

The study was published online March 2 in Frontiers of Psychiatry (doi: 10.3389/fpsyt.2021.629407).

Dr. Carter

Not a clinical diagnosis

Smartphone addiction is not formally recognized as a clinical diagnosis, but it's an "active" area of research, lead investigator Ben Carter, PhD, King's College London, noted in the report.

In a cross-sectional survey, 1,043 college students (aged 18-30 years, 73% women) completed the 10-question validated Smartphone Addiction Scale Short Version (SAS-SV) and the adapted Pittsburgh Sleep Quality Score Index.

On the SAS-SV, 406 students (38.9%) reported "addiction" to their smartphones. This estimated prevalence is consistent with other reported studies in young adult populations globally, which is in the range of 30%-45%, the researchers noted.

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years) recruited from introductory psychology courses and campus newsletters. They completed several questionnaires, including the Nomophobia Questionnaire, the Epworth Sleepiness Scale, and the Sleep Hygiene Index.

Nomophobia was prevalent, with mild, moderate, and severe nomophobia reported by 10%, 83%, and 7% of students, respectively. Only one student reported no nomophobia at all. Dr. Peszka said the fact that 89% of students had moderate or severe nomophobia is "concerning," given a 2012 study suggesting that 77% of 18- to 24-year-olds had nomophobia. This phobia "very well may be on a rapid rise," she lamented.

Greater severity of nomophobia was significantly correlated with greater sleepiness measured by both the Epworth Sleepiness Scale ($P < .05$) and the Associated Features of Poor Sleep Hygiene daytime sleepiness item ($P < .05$). More severe nomophobia was also related to decreased motivation (a commonly reported symptom of insufficient sleep) and with more maladaptive sleep hygiene behaviors (including using technology during sleep time, long daytime naps, inconsistent wake and bed times, using bed for non-sleep purposes, uncomfortable bed, and bedtime cognitive rumination).

> For now, technology is the only way some kids are going to be socializing and learning.

Prior research has shown that smartphones may lead to compulsive "checking" habits, compulsive usage, increased distress, and potentially addictive behaviors. Active phone use at bedtime has also been implicated in disrupted sleep. Nomophobia is likely to be an important consideration when treating sleep disorders and/or making any sleep hygiene recommendations, Dr. Peszka said.

Proliferation of 'night owls'

Reached for comment, Rajkumar (Raj) Dasgupta, MD, University of Southern California, Los Angeles, said this is a "very timely study with COVID-19. Right now, more than ever, technology is a double-edged sword. I'm a father of three kids and, for now, technology is the only way some kids are going to be socializing and learning."

Yet a foundation of good sleep hygiene is keeping a nightly sleep routine, said Dr. Dasgupta, who was not involved in the study. "Right now, it seems like all my sleep patients are becoming night owls and sleep time is becoming more and more delayed because there is so much news to keep up with. Also, you may be stressed at night and you may not have the motivation to wake up early in the morning."

He said it is important to counsel patients to "put technology away at night. That goes for kids and adults."

Support for the study was provided by Hendrix College Charles Brewer Fund for Psychology. Dr. Peszka and Dr. Dasgupta disclosed no relevant financial relationships.

A version of this article originally appeared on Medscape.com.

Continued from previous page

Overall, 61.6% of participants surveyed reported poor sleep; among those who reported smartphone addiction, 68.7% had poor sleep quality, vs. 57.1% of those who did not report smartphone addiction.

In multivariable analysis that adjusted for a variety of relevant factors, among those for whom there was evidence of smartphone addiction, the odds of poor sleep were increased by 41% (adjusted odds ratio [aOR] = 1.41; 95% confidence interval, 1.06-1.87; $P = .018$).

maewjpho/Thinkstock

The findings also suggest that a greater amount of time spent using the phone and greater use late at night can raise the risk for smartphone addiction.

"Should smartphone addiction become firmly established as a focus of clinical concern, those using their phones after midnight or using their phones for four or more hours per day are likely to be at high risk, and should guide administration of the SAS-SV," the researchers wrote.

Caveats, cautions, and concerns

Reached for comment, Paul Weigle, MD, psychiatrist with Hartford HealthCare and Hartford (Conn.) Hospital, and member of the American Academy of Child and Adolescent Psychiatry, said the finding of a relationship between addictive smartphone usage and poor sleep quality is not surprising.

"Great increases in adolescent screen media habits in recent decades have seen a concurrent increase in rates of insomnia among this population," he said in an interview.

Dr. Weigle also noted that young people who use the phone excessively often do so in bed, "which decreases sleep onset by disrupting conditioning (the tendency for our bodies to relate bed with sleep) and by increasing physiological arousal, which makes it more difficult to fall asleep. The blue light from smartphones used at night disrupts our body's natural circadian rhythms, confusing our brains regarding whether it is night or day, and further worsens sleep."

Dr. Weigle said in an interview that some of his patients come to him seeking sleep medications, although the best treatment is to perform a "smartphone-ectomy" every evening.

Teenage patients will "beg, borrow, or steal" to be allowed to keep their phones by the bed with the promise not to use them overnight. Three-quarters of the time, when the parents are able to charge the phone in another room, "the sleep problem resolves," Dr. Weigle said.

One caveat, he said, is that it's "somewhat unclear whether this is best classified as an addiction or simply a seriously problematic habit. Either way, this type of habit causes a great deal of distress and dysfunction in the lives of those it affects, so it is important to understand," he said.

In a statement, Bob Patton, PhD, lecturer in clinical psychology, University of Surrey, Guildford, England, noted that this is a cross-sectional study "and as such cannot lead to any firm conclusions about phone usage as the cause of reduced sleep quality.

"It does, however, provide some compelling evidence," Dr. Patton said, "that the nature of smartphone usage and its related consequences are important considerations in addressing the emerging phenomenon of 'smartphone addiction.'"

Also weighing in, Andrew Przybylski, PhD, director of research, Oxford (England) Internet Institute, University of Oxford, said the study is "the latest, among many dozens of others, to study so-called 'smartphone addiction,' a condition which is not recognized by any global health body and is not a psychiatric disorder.

"The study is a correlational analysis of a sample of participants recruited on university campuses and therefore only reflects the experiences of those who had the purpose of the study explained to them. It can say nothing about behaviors in the general population," Dr. Przybylski said in a statement.

"Readers should be cautious of making any firm conclusions about the impact of smartphone use in the general population, or the idea that they're addictive in any objective sense, on the basis of this work," he added.

The study had no specific funding. Dr. Carter, Dr. Weigle, Dr. Patton, and Dr. Przybylski have disclosed no relevant financial relationships.

A version of this article originally appeared on Medscape.com.

Use of e-cigarettes may be linked to sleep deprivation

BY RICHARD FRANKI
FROM ADDICTIVE BEHAVIORS

Current and former users of e-cigarettes are more likely to report sleep deprivation, compared with those who have never used e-cigarettes, according to the first study to evaluate the association in a large, nationally representative population of young adults.

"The e-cigarette use and sleep deprivation association seems to have a dose-response nature as the point estimate of the association increased with increased exposure to e-cigarettes," Sina Kianersi, DVM, and associates at Indiana University, Bloomington, said in Addictive Behaviors.

Sleep deprivation was 49% more prevalent among everyday users of e-cigarettes, compared with nonusers.

The investigators found that prevalence ratios for former users (1.31) and occasional users (1.25) also showed significantly higher sleep deprivation, compared with nonusers, based on a bivariate analysis of data from young adults aged 18-24 years who participated in the 2017 and 2018 Behavioral

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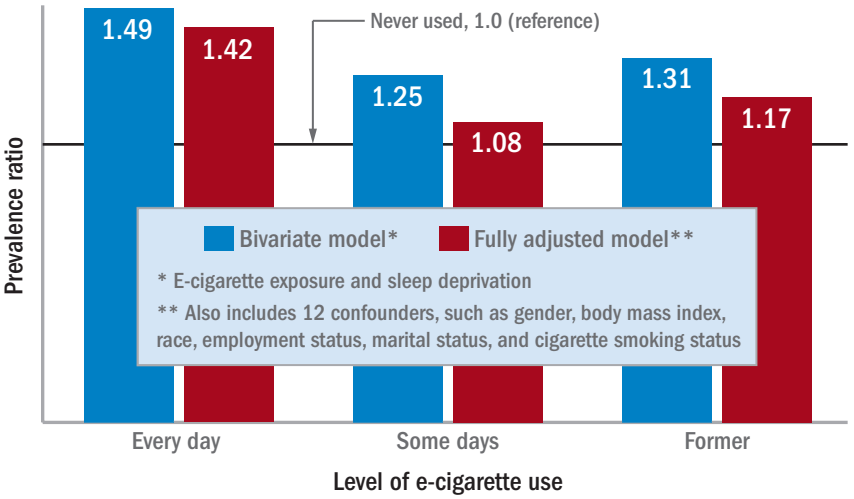
Sleep deprivation more common in e-cigarette users



MDedge News

Note: Based on data for 18,945 (bivariate) and 16,427 (fully adjusted) young adults who responded to the 2017 and 2018 Behavioral Risk Factor Surveillance System surveys.
Source: Addict Behav. 2020 Sep 6. doi: 10.1016/j.addbeh.2020.106646

Commentary by Dr. Benca

Use of e-cigarettes in adolescents and young adults is increasing dramatically. In the current study, use among the population of 18- to 24-year-olds sampled jumped from 10% in 2017 to 15.7% in 2018. Rates are even higher among younger individuals, with more than 1 in 5 high school students reporting current use of e-cigarettes.

Nicotine is a stimulant that has significant negative impacts on sleep, leading to insomnia, both at the beginning of the night (prolonged latency to sleep onset) as well as during the night (increased fragmentation of sleep and decreased sleep efficiency). It also can decrease the amount of deep slow-wave sleep. These sleep-disruptive effects can lead to sleep deprivation with resulting daytime sleepiness. Withdrawal from nicotine also leads to decreased sleep quality and daytime sleepiness, as well as increased depression.

Given that brain development continues to the middle of the third decade of life, effects of nicotine in adolescents and young adults are particularly concerning, and can lead to problems with attention, impulsivity, and anxiety. Furthermore, nicotine is a gateway drug to the use of other addictive substances. Even more alarming is that e-cigarette use is greater in individuals who are already at risk for poorer health outcomes, including those with obesity, poor mental health and depression, and alcohol abuse, which may further compound the risks of nicotine use in young people.

The current study demonstrated that in a study of more than 19,000 young adults, sleep amounts were significantly lower in those who used e-cigarettes and were lowest in those who reported daily use. Users were more likely to report a diagnosis of depression, which is also associated with sleep disturbance, but even after controlling for depression and other health and demographic confounders, daily use of e-cigarettes was associated with a 42% increased prevalence rate of obtaining less than 7 hours of sleep per night. Seven hours per night is even a likely underestimation of the average amount of sleep needed by this age group, because the recommended range is 7-9 hours per night! The additional effects of sleep deprivation in young people can further add to health risks, particularly because adolescents and young adults are even more vulnerable to the effect of sleep loss than older adults. Chronic insufficient sleep can lead to increased risk of accidents and injuries, mood dysregulation, problems with attention and memory, obesity, cardiovascular disease, metabolic syndrome, and – particularly relevant during this time of the COVID-19 pandemic – increased susceptibility to infections and decreased immune response to vaccination.

Experts advocate for the elimination of daylight saving time

BY MEGAN BROOKS
FROM SLEEP 2020

In the interest of public health and safety, the American Academy of Sleep Medicine is calling for the elimination of daylight saving time in favor of permanent year-round standard time – a recommendation that has garnered strong support from multiple medical and other high-profile organizations.

"Permanent, year-round standard time is the best choice to most closely match our circadian sleep-wake cycle," M. Adeel Rishi, MD, lead author of the AASM position statement, said in a news release. "Daylight saving time results in more darkness in the morning and more light in the evening, disrupting the body's natural rhythm," said Dr. Rishi, of the department of pulmonology, critical care, and sleep medicine, Mayo Clinic, Eau Claire, Wis., and vice chair of the AASM Public Safety Committee.

The position statement was published Aug. 26 in the Journal of Clinical Sleep Medicine (doi: 10.5664/jcsm.8780) to coincide with the virtual annual meeting of the Associated Professional Sleep Societies.

Significant health risks

In the United States, the annual "spring forward" to daylight saving time and "fall back" to standard time is required by law, although under the statute some exceptions are permitted.

There has been intense debate over the last several years about transitioning between standard and daylight saving time. The AASM says there is "an abundance of evidence" to indicate that quick transition from standard time to daylight saving time incurs significant public health and safety risks, including increased risk of heart attack, stroke, mood disorders, and car crashes.

"Although chronic effects of remaining in daylight saving time year-round have not been well studied, daylight saving time is less aligned with human circadian biology – which, because of the impacts of the delayed natural light/dark cycle on human activity, could result in circadian misalignment, which has been associated in some studies with increased cardiovascular disease risk, metabolic syndrome, and other health risks," the authors wrote.

Francesca Bellini/iStock/Getty Images

A recent study also showed an increase in medical errors in the week after switching to daylight saving time.

"Because the adoption of permanent standard time would be beneficial for public health and safety, the AASM will be advocating at the federal level for this legislative change," said AASM President Kannan Ramar, MBBS, MD, with the Mayo Clinic in Rochester, Minn.

It seems that many Americans are in favor of the change. In July, an AASM survey of roughly 2,000 U.S. adults showed that two-thirds support doing away with the seasonal

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Risk Factor Surveillance System surveys.

After adjustment for multiple confounders, young adults who currently used e-cigarettes every day were 42% more likely to report sleep deprivation than those who never used e-cigarettes, a difference that was statistically significant. The prevalence of sleep deprivation among those who used e-cigarettes on some days was not significantly higher (prevalence ratio, 1.08), but the ratio between former users and never users was a significant 1.17, the investigators said.

"The nicotine in the inhaled e-cigarette aerosols may have negative effects on sleep architecture and disturb the neurotransmitters that regulate sleep cycle," they suggested, and because higher doses of nicotine produce greater reductions in sleep duration, "those who use e-cigarette on a daily basis might consume higher doses of nicotine, compared to some days, former, and never users, and therefore get fewer hours of sleep."

Nicotine withdrawal, on the other hand, has been found to increase sleep duration in a dose-dependent manner, which "could explain the smaller [prevalence ratios] observed for the association between e-cigarette use and sleep deprivation among former and some days e-cigarette users," Dr. Kianersi and associates added.

The bivariate analysis involved 18,945 survey respondents, of whom 16,427 were included in the fully adjusted model using 12 confounding factors.

The authors of the paper disclosed no conflicts of interest.

Insomnia may have a role in generation of stressful life events

BY CHRISTINE KILGORE
FROM SLEEP 2020

Insomnia disorder appears to play a causal role in the development of new stressful life events, especially "dependent" events for which individuals are at least partly responsible, said the investigators of an ongoing longitudinal study of people who have experienced involuntary job loss.

The "stress-generation hypothesis" has been applied for several decades in the context of depression. It posits that depressed individuals generate more stressful life events – events that create family conflict or disrupt careers, for instance – than individuals who are not depressed.

The new analysis of individuals with involuntary job loss suggests that the same can be said of insomnia. "Insomnia disorder is associated with fatigue, daytime sleepiness, impaired concentration, and difficulties in emotional regulation," Iva Skobic, MSPH, MA, a PhD student at the University of Arizona, Tucson, said at the virtual annual meeting of the Associated Professional Sleep Societies.

"These may lead to impaired decision-making, interpersonal conflicts, difficulty meeting deadlines and keeping commitments, and other sources [of stressful life events]," she said. "This extension of the stress-generation hypothesis has important implications for harm reduction interventions for insomnia disorder."

Investigators conducted a cross-lagged panel analysis using baseline and 3-month follow-up data from 137 individuals who completed a standardized, textual life event measure called the Life Events and Difficulties Schedule after having lost their jobs involuntarily. Participants were interviewed and their events were rated for severity by a consen-

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time change. Only 11% opposed it. In addition, the academy's 2019 survey showed more than half of adults feel extremely, or somewhat, tired after the springing ahead to daylight saving time.

Strong support

The position statement has been endorsed by 19 organizations, including the American Academy of Cardiovascular Sleep Medicine, American College of Chest Physicians, American College of Occupational and Environmental Medicine, National PTA, National Safety Council, Society of Anesthesia and Sleep Medicine, and the Society of Behavioral Sleep Medicine.

Weighing in on the issue, Saul Rothenberg, PhD, from the Sleep Center at Greenwich Hospital, Conn., said the literature on daylight saving time has grown over the past 20 years. He said he was "humbled" by the research that shows that a "relatively small" misalignment of biological and social clocks has a measurable impact on human health and behavior.

"Because misalignment is associated with negative health and performance outcomes, keeping one set of hours year-round is promoted to minimize misalignment and associated consequences," he added.

In light of this research, the recommendation to dispense with daylight saving time seems "quite reasonable" from a public health perspective. "I am left with a strengthened view on the importance of regular adequate sleep as a way to enhance health, performance, and quality of life," he added.

This research had no commercial funding. Dr. Rishi and Dr. Rothenberg have disclosed no relevant financial relationships.

A version of this article originally appeared on Medscape.com.

Commentary by Dr. Sundar

Living creatures have developed biological rhythms that are adapted to the 24-hour rotation of the earth. The sleep-wake cycle is the dominant circadian and, like all biological and behavioral rhythms, sleep is regulated by transcriptional-translational feedback loops. In fact, up to 43% of protein-coding genes in mammals show circadian rhythms (Proc Natl Acad Sci USA. 2014;111[45]:16219-24) and changes in sleep duration and timing can have profound effects on both central and peripheral clock genes (J Sleep Res. 2015;24:476-93).

Given the widespread effects of clock gene outputs on protein expression, the effects of clock misalignment from shift to daylight saving time (DST) in not unexpected. Even a 1-hour shift in time change is associated with increased risk of myocardial infarctions and strokes in the first few days after DST begins (Int Emerg Med. 2018;13:641-6) and worsening of inflammatory bowel disease and depression in the fall (Front Med. 2019;6:103). There is now widespread recognition of adverse health effects of DST amongst health professionals and societies along with increasing advocacy for a need for legislative change for public health and safety. This statement by the American Academy of Sleep Medicine is timely and both medical professionals and lay public should vigorously support the push to eliminate DST.

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sus panel using operationalized criteria. The analysis employed linear regression controlling for covariates (age, gender, and race) and logistic regression that controlled for insomnia at baseline. Insomnia disorder was defined as meeting ICSD-2/3 criteria using the Duke Structured Interview for Sleep Disorders.

The findings: Insomnia disorder at baseline predicted the number of stressful life events (either dependent or interpersonal) generated within 3 months (beta, 0.70; standard error, 0.31; T score, 2.27; $P = .03$). Conversely, the number of stressful events at baseline did not predict insomnia (odds ratio, 0.97; 95% confidence interval, 0.73-1.29). There also was a trend toward increased generation of dependent events specifically among those with insomnia disorder.

Participants were a mean age of 42 years, and all had been in their previous place of employment for at least 6 months. Nearly 60% met the diagnostic threshold for insomnia at baseline. They were part of a larger ongoing study examining the linkages between job loss and sleep disturbances, obesity, and mental health – the Assessing Daily Activity Patterns through Occupational Transitions (ADAPT) study, supported by the National Heart, Lung, and Blood Institute.

This analysis on insomnia was completed before the COVID-19 pandemic began, but it and other analyses soon to be reported are highly relevant to the economic climate, said Patricia Haynes, PhD, principal investigator of ADAPT and a coauthor of the insomnia study, in an interview after the meeting.

Insomnia is a frequent comorbidity of depression and shares many of its symptoms, from increased fatigue to emotional dysregulation and an increased risk of maladaptive coping strategies. "Interestingly, the literature on the stress-generation hypothesis posits that these very symptoms are on the casual pathway between depression and stressful life events," said Ms. Skobic at the meeting.

In commenting on the study, Krishna M. Sundar, MD, medical director of the Sleep-Wake Center at the University of Utah, Salt Lake City, noted that the analysis did not include any measure of the severity of insomnia. Still, he said, "finding an association [with stress generation] at [just] 3 months with the presence of insomnia disorder is quite interesting."

There were higher rates of insomnia in the sample than depression, Dr. Haynes said, but the analysis did not control for depression or take it into account.

"We know [from prior research] that stress clearly leads to insomnia. The big [takeaway] here is that insomnia can also lead to more stress," she said. "It's important to think of it as a reciprocal relationship. If we can potentially treat insomnia, we may be able to stop that cycle of other stressful events that affect both [the individuals] and others as well."

Ms. Skobic had no disclosures.

Commentary by Dr. Benca

Job loss is one of the 10 most stressful life events, and more than 20 million Americans have lost their jobs as a result of the COVID-19 pandemic. It is, unfortunately, only one of many stressors affecting the population during the current pandemic and leading to widespread insomnia, or "coronasomnia."

Most of us have experienced how a stressful event can disrupt our sleep, and how we are more irritable and vulnerable to stress following a bout of insomnia. That is because one of the functions of sleep is to downregulate our experiences of emotional distress, and both insomnia and sleep loss lead to a decrease in our ability to have a more positive emotional response to a positive event.

To make matters worse, individuals prone to insomnia tend to have greater sleep disruption during stressful situations, and show physiological evidence of hyperarousal during both waking and sleep, as well as increased emotional reactivity. Insomnia is also closely linked to depression, with individuals experiencing chronic insomnia having a significantly greater risk of developing depression. Furthermore, like those with insomnia, depressed individuals also show increased stress reactivity, which could also be contributing to the findings noted in this study, as the analysis did not control for depressive symptoms.

The important finding in this study, however, is that baseline insomnia predicted increased stressful life events, particularly those that were "dependent" and thus presumably somewhat under subjects' control. This is consistent with other studies that have reported that poor sleep was predictive of more work and family conflict the following day.

The interesting thing about the design of the current study is that all the subjects had recently experienced involuntary job loss, a major life stressor, but not all of them had insomnia. Those with insomnia at the time of study entry reported significantly more stressful life events in the subsequent 3 months. This suggests that the lack of insomnia in some individuals after job loss indicated a greater level of resilience and thus better ability to cope with ongoing life challenges. There is also evidence that better sleep and/or successful treatment of insomnia may improve daytime emotional function and decrease the likelihood of becoming entangled in stressful interactions and events. Thus the findings overall suggest a bidirectional relationship between stress and insomnia, whereby increasing either component exacerbates the other, and conversely, decreasing either component can improve the other.

In the current pandemic, there has been a dramatic increase in major life stressors experienced by a large segment of the population. Not surprisingly, those living and working in more stressful situations (for example, essential workers, those from lower socioeconomic levels, and minorities) have shown increased rates of insomnia. Results from this study suggest that they may be more vulnerable to experiencing increased stressful life events and more vulnerable to psychiatric disorders, highlighting the need for health care providers to assess sleep problems routinely.

Treating insomnia, anxiety in pregnancy and postpartum period in pandemic

BY LEE S. COHEN, MD

Since the start of the pandemic, we have been conducting an extra hour of Virtual Rounds at the Center for Women's Mental Health. Virtual Rounds has been an opportunity to discuss cases around a spectrum of clinical management issues with respect to depression, bipolar disorder, and a range of anxiety disorders like obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and generalized anxiety disorder. How to apply the calculus of risk-benefit decision-making around management of psychiatric disorders during pregnancy and the postpartum period has been the cornerstone of the work at our center for over 2 decades.

When we went virtual at our center in the early spring, we decided to keep the format of our faculty rounds the way they have been for years and to sustain cohesiveness of our program during the pandemic. But we thought the needs of pregnant and postpartum women warranted being addressed in a context more specific to COVID-19, and also that reproductive psychiatrists and other clinicians could learn from each other about novel issues coming up for this group of patients during the pandemic. With that backdrop, Marlene Freeman, MD, and I founded "Virtual Rounds at the Center" to respond to queries from our colleagues across the country; we do this just after our own rounds on Wednesdays at 2:00 p.m.

As the pandemic has progressed, Virtual Rounds has blossomed into a virtual community on the Zoom platform, where social workers, psychologists, nurse prescribers, psychiatrists, and obstetricians discuss the needs of pregnant and postpartum women specific to COVID-19. Frequently, our discussions involve a review of the risks and benefits of treatment before, during, and after pregnancy.

Seemingly, week to week, more and more colleagues raise questions about the treatment of anxiety and insomnia during pregnancy and the postpartum period. I've spoken in previous columns about the enhanced use of telemedicine. Telemedicine not only facilitates efforts like Virtual Rounds and our ability to reach out to colleagues across the country and share cases, but also has allowed us to keep even closer tabs on the emotional well-being of our pregnant and postpartum women during COVID-19.

The question is not just about the effects of a medicine that a woman might take to treat anxiety or insomnia during pregnancy, but the experience of the pandemic per se, which we are measuring in multiple studies now using a variety of psychological instruments that patients complete. The pandemic is unequivocally taking a still unquantified toll on the mental health of Americans and potentially on the next generation to come.

Midcycle awakening during pregnancy

Complaints of insomnia and midcycle awakening during pregnancy are not new – it is the rule, rather than the exception for many pregnant women, particularly later in pregnancy. We have unequivocally seen a worsening of complaints of sleep disruption including insomnia and midcycle awakening during the pandemic that is greater than what we have seen previously. Both patients and colleagues have asked us the safest ways to manage it. One of the first things we consider when we hear about insomnia is whether it is part of an underlying mood disorder. While we see primary insomnia clinically, it really is important to remember that insomnia can be part and parcel of an underlying mood disorder.

Dr. Cohen is the director of the Ammon-Pinizzotto Center for Women's Mental Health at Massachusetts General Hospital (MGH) in Boston, which provides information resources and conducts clinical care and research in reproductive mental health. He has been a consultant to manufacturers of psychiatric medications.

With that in mind, what are the options? During the pandemic, we've seen an increased use of digital cognitive behavioral therapy for insomnia (CBT-I) for patients who cannot initiate sleep, which has a very strong evidence base for effectiveness as a first-line intervention for many.

If a patient has an incomplete response to CBT-I, what might be pursued next? In our center, we have a low threshold for using low doses of benzodiazepines, such as lorazepam or clonazepam, because the majority of data do not support an increased risk of major congenital malformations even when used in the first trimester. It is quite common to see medicines such as newer nonbenzodiazepine sedative hypnotics such as Ambien CR (zolpidem) or Lunesta (eszopiclone) used by our colleagues in ob.gyn. The reproductive safety data on those medicines are particularly sparse,

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and they may have greater risk of cognitive side effects the next day, so we tend to avoid them.

Another sometimes-forgotten option to consider is using low doses of tricyclic antidepressants (that is, 10-25 mg of nortriptyline at bedtime), with tricyclics having a 40-year history and at least one pooled analysis showing the absence of increased risk for major congenital malformations when used. This may be a very easy way of managing insomnia, with low-dose tricyclics having an anxiolytic effect as well.

Anxiety during pregnancy

The most common rise in symptoms during COVID-19 for women who are pregnant or post partum has been an increase in anxiety. Women present with a spectrum of concerns leading to anxiety symptoms in the context of the pandemic. Earlier on in the pandemic, concerns focused mostly on how to stay healthy, and how to mitigate risk and not catch SARS-CoV-2 during pregnancy, as well as the very complex issues that were playing out in real time as hospital systems were figuring out how to manage pregnant women in labor and to keep both them and staff safe. Over time, anxiety has shifted to still staying safe during the pandemic and the potential impact of SARS-CoV-2 infection on pregnancy outcomes. The No. 1 concern is what the implications of COVID-19 disease are on mother and child. New mothers also are anxious about how they will practically navigate life with a newborn in the postpartum setting.

Early on in the pandemic, some hospital systems severely limited who was in the room with a woman during labor, potentially impeding the wishes of women during delivery who would have wanted their loved ones and/or a doula present, as an example. With enhanced testing available now, protocols have since relaxed in many hospitals to allow partners – but not a team – to remain in the hospital during the labor process. Still, the prospect of delivering during a pandemic is undoubtedly a source of anxiety for some women.

This sort of anxiety, particularly in patients with preexisting anxiety disorders, can be particularly challenging. Fortunately, there has been a rapid increase over the last several years of digital apps to mitigate anxiety. While many of them have not been systematically studied, the data on biobehavioral intervention for anxiety is enormous, and this should be used as first-line treatment for patients with mild to moderate symptoms; so many women would prefer to avoid pharmacological intervention during pregnancy, if possible, to avoid fetal drug exposure. For patients who meet criteria for frank anxiety disorder, other nonpharmacologic interventions such as CBT have been shown to be effective.

Frequently, we see women who are experiencing levels of anxiety where nonpharmacological interventions have an incomplete response, and colleagues have asked about the safest way to treat these patients. As has been discussed in multiple previous columns, selective serotonin reuptake inhibitors (SSRIs) should be thought of sooner rather than later, particularly with medicines with good reproductive safety data such as sertraline, citalopram, or fluoxetine (N Engl J Med. 2014 Jun 19; 370(25):2397-407).

We also reported over 15 years ago that at least 30%-40% of women presenting with histories of recurrent major depression at the beginning of pregnancy had comorbid anxiety disorders, and that the use of benzodiazepines in that population in addition to SSRIs was exceedingly common, with doses of approximately 0.5-1.5 mg of clonazepam or lorazepam being standard fare. Again, this is very appropriate treatment to mitigate anxiety symptoms because now have enough data as a field that support the existence of adverse outcomes associated with untreated anxiety during pregnancy in terms of both adverse obstetric and neonatal outcomes, higher rates of preterm birth, and other obstetric complications. Hence, managing anxiety during pregnancy should be considered like managing a toxic exposure – the same way that one would be concerned about anything else that a pregnant woman could be exposed to.

Lastly, although no atypical antipsychotic has been approved for the

treatment of anxiety, its use off label is extremely common. More and more data support the absence of a signal of teratogenicity across the family of molecules including atypical antipsychotics. Beyond potential use of atypical antipsychotics, at Virtual Rounds last week, a colleague asked about the use of gabapentin in a patient who was diagnosed with substance use disorder and who had inadvertently conceived on gabapentin, which was being used to treat both anxiety and insomnia. We have typically avoided the use of gabapentin during pregnancy because prospective data have been limited to relatively small case series and one report, with a total of exposures in roughly the 300 range.

However, our colleagues at the Harvard School of Public Health have recently published an article that looked at the United States Medicaid Analytic eXtract (MAX) dataset, which has been used to publish other articles addressing atypical antipsychotics, SSRIs, lithium, and pharmacovigilance investigations among other important topics. In this study, the database was used to look specifically at 4,642 pregnancies with gabapentin exposure relative to 1,744,447 unexposed pregnancies, without a significant finding for increased risk for major congenital malformations (PLOS Med. 2020 Sep 1;17(9):e1003322).

The question of an increased risk of cardiac malformations and of increased risk for obstetric complications are difficult to untangle from anxiety and depression, as they also are associated with those same outcomes. With that said, the analysis is a welcome addition to our knowledge base for a medicine used more widely to treat symptoms such as anxiety and insomnia in the general population, with a question mark around where it may fit into the algorithm during pregnancy.

In our center, gabapentin still would not be used as a first-line treatment for the management of anxiety or insomnia during pregnancy. But these new data still are reassuring for patients who come in, frequently with unplanned pregnancies. It is an important reminder to those of us taking care of patients during the pandemic to review use of contraception, because although data are unavailable specific to the period of the pandemic, what is clear is that, even prior to COVID-19, 50% of pregnancies in America were unplanned. Addressing issues of reliable use of contraception, particularly during the pandemic, is that much more important.

In this particular case, our clinician colleague in Virtual Rounds decided to continue gabapentin across pregnancy in the context of these reassuring data, but others may choose to discontinue or pursue some of the other treatment options noted above.

Commentary by Dr. Benca

The COVID-19 pandemic has had a significant impact on sleep and mental health in people worldwide. COVID-19 infection can lead to insomnia and new onset of psychiatric illness. But the effects of the pandemic go far beyond those who have been infected – multiple studies have shown persistently increased rates of insomnia, anxiety, and depression in the worldwide population at large. Young people; essential workers; underrepresented minorities; and those who have experienced job loss, financial loss, or loss of a loved one from COVID-19 are especially at risk.

Not surprisingly, rates of insomnia and psychological distress have also increased in pregnant women during the COVID-19 pandemic, possibly even more so than in the general population. A recent meta-analysis of 23 studies estimated rates of anxiety (37%), depression (31%), psychological distress (70%), and insomnia (49%) in pregnant women, as well as postpartum depression (22%) during the pandemic (Front Psychol. 2020 Nov 25;11:617001. doi: 10.3389/fpsyg.2020.617001). Given these numbers, it is imperative that pregnant and postpartum women are regularly screened for sleep problems and psychiatric symptoms.

Insomnia during pregnancy not only increases the likelihood for postpartum depression but also is associated with other poor health outcomes in mothers and infants, including increased rates of preterm birth and large-for-gestational-age infants. Anxiety and depression during pregnancy are associated with threats to maternal and fetal health, including gestational hypertension, preeclampsia, miscarriage, preterm birth, low birth weight, as well as worse cognitive and emotional development in infants and children.

Pregnancy is thus a time of increased risk for both sleep and psychiatric problems that can significantly impact the health of both mother and baby. Women receiving prenatal care potentially results in more of these disorders being identified and treated. The Virtual Rounds at the Center for Women's Mental Health developed by Dr. Cohen is a model that can hopefully be adopted in other medical centers to help health care providers identify and manage psychiatric care during pregnancy, particularly during this time of the COVID-19 pandemic. A major issue in treating psychiatric disorders in pregnant women is that there are essentially no controlled studies on the safety and efficacy of psychotropic medications in this population. The Virtual Rounds gives experts the ability to share valuable information about their experiences treating anxiety and insomnia in pregnant patients.

Dr. Cohen makes the important point that, for mothers and infants, it's far less dangerous for mothers to use pharmacologic treatments for major psychiatric disorders than for mothers to not take them, because of the potential effects of the disorders themselves. Finally, the use of video telemedicine and digital cognitive-behavioral therapy, not only for insomnia but also for depression, has increased dramatically during the pandemic, has generally good patient acceptance, and is likely to become a major component of the "new normal" in behavioral health care.

Insomnia + COPD tied to more health care use

BY CHRISTINE KILGORE
FROM SLEEP 2020

Insomnia is "highly prevalent" in veterans with chronic pulmonary obstructive disease and is significantly associated with greater COPD-related health care utilization, according to an analysis of national Veterans Health Administration data.

"The study highlights the importance of exploring potential sleep disturbances and disorders in this population and suggests that a targeted treatment for insomnia may help to improve COPD outcomes in veterans with COPD and insomnia," said Faith Luyster, PhD, assistant professor at the University of Pittsburgh, in an interview after the virtual annual meeting of the Associated Professional Sleep Societies, where she presented the findings.

Dr. Luyster and coinvestigators used an administrative database from the Veterans Affairs Corporate Data Warehouse to identify more than 1.5 million patients with COPD who used VHA services over a 6-year period (fiscal years 2011-2017). Insomnia was defined by ICD-9/10 diagnostic codes and/or a sedative-hypnotic prescription for at least 30 doses during any of these years.

Insomnia with COPD was prevalent in this sample of veterans at 37.3%. Compared with veterans without comorbid insomnia, those who had both COPD and insomnia (575,539 of the total 1,542,642) were older (69 vs. 64 years), more likely to be female (6.3% vs. 3.7%), more likely to be Black (14% vs. 11%), and more likely to be a current smoker (46.1% vs. 35.5%).

Those with both COPD and insomnia were also more likely to have a service-connected disability rating of 50% of greater; use supplemental oxygen; be divorced, widowed, or separated; have a higher body mass index; or have other medical or psychiatric conditions – in particular obstructive sleep apnea (39% vs. 7%), depression (21% vs. 5%), and PTSD (33% vs. 3%).


Dr. Ioachimescu

P values were < .001 for all of these demographic and clinical variables, Dr. Luyster reported at the meeting.

Comorbid insomnia clearly affected health care utilization, she said. Veterans with insomnia in addition to COPD had more outpatient and ED visits (10.5 vs. 6.9, and 1.6 vs. 1.4, respectively) and more hospitalizations (2.2 vs. 1.8) with a primary diagnostic code for COPD or COPD exacerbation ($P < .001$).

A negative binomial regression analysis ($P < .001$) showed that "even after controlling for demographic and other medical conditions, COPD patients with insomnia had greater rates of health care utilization relative to COPD patients without insomnia," Dr. Luyster said in the interview.

Prior studies have suggested that disturbed sleep is a predictor of poorer longitudinal outcomes in COPD, even after controlling for COPD severity, but have not looked specifically at insomnia, she said.

Commenting on the study Octavian C. Ioachimescu, MD, PhD, of Emory University, Atlanta, and the Atlanta VA Medical Center in Decatur, said the criteria used to define insomnia – unadjudicated ICD diagnoses as well as sedative-hypnotic prescriptions – may explain part of the reported prevalence of insomnia. Even so, the findings add to existing literature demonstrating that COPD and insomnia are both common disorders among VHA patients, and that their frequent coexistence "could have adverse consequences on the overall health, functional status, long-term outcomes, and quality of life of these patients."

Questions of causation are yet to be answered, he said. "Is it that uncontrolled or severe airflow ob-

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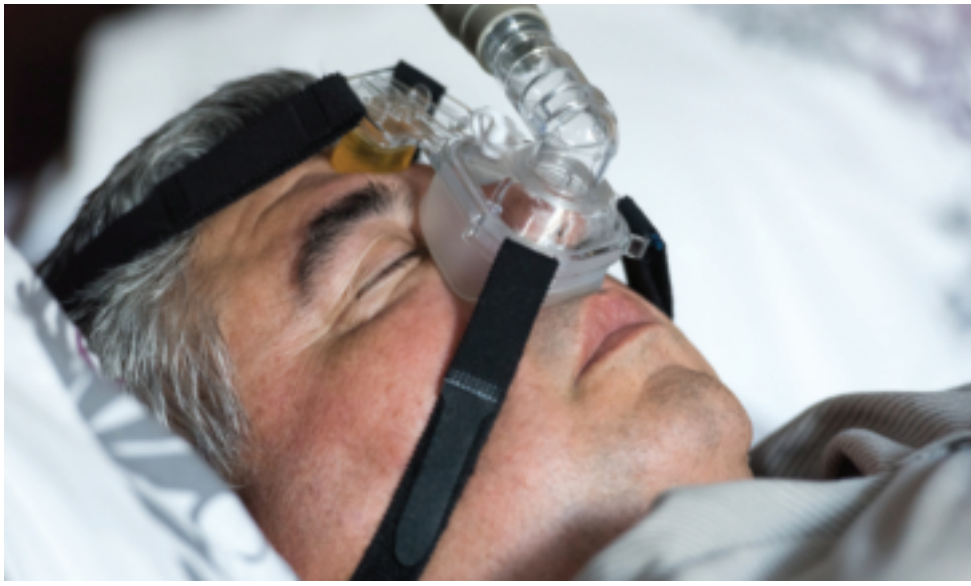
Commentary by Dr. Sundar

A number of studies have highlighted the importance of sleep disturbances in patients with chronic obstructive pulmonary disease (COPD) and linked it to health status, quality of life scores, symptoms of dyspnea and fatigue, and risk of COPD exacerbations. Whereas there has been focus on comorbid obstructive sleep apnea (McNicholas WT et al. Eur Respir Rev. 2019;28:190064), the prevalence of insomnia in COPD patients is significant, affecting at least a quarter or more patients with COPD (Budhiraja R et al. Sleep. 2012;35(3):369-75). Luyster and colleagues' study on a large sample of veterans with COPD over a 6-year period confirms the high prevalence of insomnia in patients with COPD. It also shows that insomnia in COPD was associated not only with medical and psychiatric comorbidities but also with increased health care utilization.

While causative factors for insomnia in COPD are many, poor sleep quality as assessed by validated questionnaires such as the Pittsburgh sleep quality index has been consistently shown to be associated with an increased risk of exacerbations (Shorofsky M et al. Chest. 2019:156:852-63). Therefore, frequent nighttime symptom burden coupled with sleep disturbance represents a modifiable risk factor in patients with COPD (Zeidler MR et al. Sleep. 2018;1:41(5);zsy044). Routine evaluation for sleep quality and assessment for factors driving insomnia should be done in patients with COPD. Addressing insomnia in conjunction with sleep-disordered breathing offers the opportunity to improve COPD outcomes.

Study validates OSA phenotypes in Latinos

BY CHRISTINE KILGORE
REPORTING FROM SLEEP 2020


Juanmonino/E+/Getty Images

Three previously described clinical phenotypes of obstructive sleep apnea (OSA) have been validated in a large and diverse Hispanic/Latino community-based population for the first time, according to findings presented at the virtual annual meeting of the Associated Professional Sleep Societies.

The three OSA symptom profiles present in this population – labeled "minimally symptomatic," "disturbed sleep," and "daytime sleepiness" – are consistent with recent findings from the Sleep Apnea Global Interdisciplinary Consortium, which were published in Sleep (2018 Mar. doi: 10.1093/sleep/zsx214), but there are notable differences in the prevalence of these clusters, with the minimally symptomatic cluster much more prevalent than in prior research, reported Kevin Gonzalez, of the University of California, San Diego.

"Other biopsychosocial factors may be contributing to OSA phenotypes among Hispanics and Latinos," Mr. Gonzalez said in his presentation. Prior research to characterize the heterogeneity of sleep apnea has not included a diverse Latino population, he emphasized.

The adults studied were aged 18-74 years and participants in the multisite Hispanic Community Health Study/Study of Latinos (HCHS/SOL), a comprehensive study of Hispanic/Latino health and disease in the United States. Their respiratory events were measured overnight in HCHS/SOL sleep reading centers with an ARES Unicorder 5.2, B-Alert. Sleep patterns and risk factors were assessed using the Sleep Heart Health Study Sleep Habits Questionnaire and the Epworth Sleepiness Scale.

Participants meeting the criteria for moderate to severe OSA (with an Apnea Hypopnea Index of 15 or above) were included in the analysis (n = 1,623). Their average age was 52.4 ± 13.9 years, and 34.1% were female.

To identify phenotype clusters, investigators performed a latent class analysis using 15 common OSA symptoms and a survey weighted to adjust for selection bias. The three clusters offering the "best" fit for the data aligned with the previously reported phenotypes and identified daytime sleepiness in 15.3%, disturbed sleep (insomnia-like symptoms) in 37.7%, and minimally symptomatic (a low symptom profile) in 46.9%.

These phenotypes were reported in the European Respiratory Journal in 2014 in a cluster analysis of data from a sleep apnea cohort in Iceland (2014 Dec;44[6]:1600-7) and later replicated in the analysis of data from the Sleep Apnea Global Interdisciplinary Consortium published in Sleep in 2018. The consortium study also added two additional phenotypes, labeled "upper airway symptoms dominant"

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struction causing frequent nocturnal arousals, dyspnea, orthopnea, overuse of inhaled sympathomimetics and heightened anxiety leads to insomnia? Or is it that insomnia – possibly in a cluster with other affective disorders such as depression, anxiety disorders, or PTSD – elicits more frequent or more severe symptoms of shortness of breath in those with smoking-induced airway and parenchymal lung disease, making the latter diagnosis more overt than in others?

"My bet is on a bidirectional causal relationship," said Dr. Ioachimescu, an editorial board advisor of CHEST Physician.

"Regardless of the etiology [of insomnia in veterans with COPD]," Dr. Luyster said, "it's important that [insomnia] be addressed and treated appropriately, whether that be through pharmacological treatment, or probably more ideally through [cognitive behavioral therapy] for insomnia."

The study did not control for COPD severity, she said, because of the difficulty of extracting this data from the VA Corporate Data Warehouse. The study was funded by the VA Competitive Career Development Fund.

Dr. Luyster reported that she had no disclosures. Dr. Ioachimescu also said he had no relevant disclosures.

Study confirms link between PAP apnea treatment and dementia onset

BY CHRISTINE KILGORE
FROM SLEEP 2020

Obstructive sleep apnea (OSA) treatment with positive airway pressure (PAP) therapy was associated with lower odds of incident Alzheimer's disease and other dementia in a large retrospective cohort study of Medicare patients with the sleep disorder.

The study builds on research linking OSA to poor cognitive outcomes and dementia syndromes. With use of a 5% random sample of Medicare beneficiaries (more than 2.7 million) and their claims data, investigators identified approximately 53,000 who had an OSA diagnosis prior to 2011.

Of these Medicare beneficiaries, 78% with OSA were identified as "PAP-treated" based on having at least one durable medical equipment claim for PAP equipment. And of those treated, 74% were identified as "PAP adherent" based on having more than two PAP equipment claims separated by at least a month, said Galit Levi Dunietz, PhD, MPH, at the virtual annual meeting of the Associated Professional Sleep Societies.

Dr. Dunietz and her coinvestigators used logistic regression to examine the associations between PAP treatment and PAP treatment adherence, and incident ICD-9 diagnoses of Alzheimer's disease (AD), mild cognitive impairment (MCI), and dementia not otherwise specified (DNOS) over the period 2011-2013.

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and "sleepiness dominant."

The prevalence of a "minimally symptomatic group" in the new analysis of the Hispanics/Latinos in the United States is much higher than reported in these prior studies, at least partly, the investigators believed, because the "prior studies were clinical samples, and the people who were minimally symptomatic didn't get to the sleep centers," Mr. Gonzalez said in an interview after the meeting.

Patients with a phenotype of daytime sleepiness – the most common phenotype in prior research – constituted only a minority in the Hispanic/Latino population, he said.

Alberto Ramos, MD, of the University of Miami and the principal investigator, said in an interview that the research team is currently analyzing "if and how these different [phenotypic] clusters could affect the incidence of comorbidities" recorded in the HCHS/SOL study, such as hypertension, diabetes, cardiovascular disease, and cognitive decline.

For now, he said, the findings suggest that OSA may be especially underrecognized in Hispanics and Latinos and that there is more research to be done to better identify and stratify patients with varying symptomatology for more personalized treatment and for clinical trial selection. "Maybe we should expand our criteria ... broaden our [recognition] of the presentation of sleep apnea and the symptoms associated with it, not only in Hispanics but maybe in the general population," Dr. Ramos said.

The investigators reported no relevant disclosures.

Commentary by Dr. Sundar:

Obstructive sleep apnea is a condition with a high prevalence in the general population, and given its protean effects on health, its recognition across populations is important. While clinical assessments are aimed at predicting how likely someone is to have OSA on objective testing, the pattern of symptoms from untreated OSA can also be predictive of outcomes. This was first reported in an Icelandic study (Ye et al. Eur Respir J. 2014;44:1600-7), following which the applicability of using symptom-based clustering to look at outcomes has been expanded to a number of different populations (Sleep Apnea Global International Consortium (SAGIC) cluster analysis – Keenan et al. Sleep. 2018;1-14). This has allowed the appreciation of cultural and psychosocial factors critical in expression and detection of OSA. Initial data on OSA prevalence from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) have shown that while a quarter of patients met criteria for sleep-disordered breathing, only 1.3% had a sleep apnea diagnosis (Redline S et al. Am J Respir Crit Care Med. 2014;189:335-44). The finding of the current cluster analysis further expands upon prior studies showing that the "minimally symptomatic" cluster in the HCHS/SOL study was higher in the Hispanic/Latino population as compared to the Icelandic and different SAGIC population studies. This has implications for both outcomes and treatment of OSA in this population.

In terms of outcomes, there were differences between association with comorbidities in the "minimally symptomatic" cluster noted between Icelandic and SAGIC studies – such relationship needs to be derived from the HCHS/SOL cohort. In terms of treatment, while all clusters respond to treatment with CPAP, there may be variations in treatment adherence between different clusters with the "excessively sleepy" cluster being more adherent compared to the "disturbed sleep" cluster, further highlighting the need to understand the distribution of symptom clusters in individual ethnic groups.

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After adjustments for potential confounders (age, sex, race, stroke, hypertension, cardiovascular disease, and depression), OSA treatment was associated with a significantly lower odds of a diagnosis of AD (odds ratio, 0.78; 95% confidence interval 0.69-0.89) or DNOS (OR, 0.69; 95% CI, 0.55-0.85), as well as nonsignificantly lower odds of MCI diagnosis (OR, 0.82; 95% CI, 0.66-1.02).

"People who are treated for OSA have a 22% reduced odds of being diagnosed with AD and a 31% reduced odds of getting DNOS," said Dr. Dunietz, from the University of Michigan in Ann Arbor, in an interview after the meeting. "The 18% reduced odds of mild cognitive disorder is not really significant because the upper bound is 1.02, but we consider it approaching significance."

Adherence to treatment was significantly associated with lower odds of AD, but not with significantly lower odds of DNOS or MCI, she said. OSA was confirmed by ICD-9 diagnosis codes plus the presence of relevant polysomnography current procedural terminology code.

> "We should be thinking of doing honest and rigorous clinical trials for sleep apnea with cognitive outcomes."

All told, the findings "suggest that PAP therapy for OSA may lower short-term risk for dementia in older persons," Dr. Dunietz and her coinvestigators said in their poster presentation. "If a causal pathway exists between OSA and dementia, treatment of OSA may offer new opportunities to improve cognitive outcomes in older adults with OSA."

Andrew W. Varga, MD, of the division of pulmonary, critical care, and sleep medicine at the Icahn School of Medicine at Mount Sinai and the Mount Sinai Integrative Sleep Center, both in New York, said that cognitive impairment is now a recognized clinical consequence of OSA and that OSA treatment could be a target for the prevention of cognitive impairment and Alzheimer's disease in particular.

"I absolutely bring it up with patients in their 60s and 70s. I'm honest – I say, there seems to be more and more evidence for links between apnea and Alzheimer's in particular. I tell them we don't know 100% whether PAP reverses any of this, but it stands to reason that it does," said Dr. Varga, who was asked to comment on the study and related research.

An analysis published several years ago in Neurology from the Alzheimer's Disease Neuroimaging Initiative cohort found that patients with self-reported sleep apnea had a younger age of MCI or AD onset (about 10 years) and that patients who used continuous positive airway pressure had a delayed age of onset (2015;84[19]:1964-71). "Those who had a subjective diagnosis of sleep apnea and who also reported using CPAP as treatment seemed to go in the opposite direction," said Dr. Varga, a coauthor of that study. "They had an onset of AD that looked just like people who had no sleep apnea."

While this study was limited by sleep apnea being self-reported – and by the lack of severity data – the newly reported study may be limited by the use of ICD codes and the fact that OSA is often entered into patient's chart before diagnosis is confirmed through a sleep study, Dr. Varga said.

"The field is mature enough that we should be thinking of doing honest and rigorous clinical trials for sleep apnea with cognitive outcomes being a main measure of interest," he said. "The issue we're struggling with in the field is that such a trial would not be short."

There are several theories for the link between OSA and cognitive impairment, he said, including disruptions in sleep architecture leading to increased production of amyloid and tau and/or decreased "clearance" of extracellular amyloid, neuronal sensitivity to hypoxia, and cardiovascular comorbidities.

Dr. Dunietz's study was supported by the American Academy of Sleep Medicine Foundation. She reported having no disclosures. Dr. Varga said he has no relevant disclosures.

Commentary by Dr. Sundar

A number of studies have highlighted the importance of sleep disturbances in patients with chronic obstructive pulmonary disease (COPD) and linked it to health status, quality of life scores, symptoms of dyspnea and fatigue, and risk of COPD exacerbations. Whereas there has been focus on comorbid obstructive sleep apnea (McNicholas WT et al. Eur Respir Rev. 2019;28:190064), the prevalence of insomnia in COPD patients is significant, affecting at least a quarter or more patients with COPD (Budhiraja R et al. Sleep. 2012;35(3):369-75). Luyster and colleagues' study on a large sample of veterans with COPD over a 6-year period confirms the high prevalence of insomnia in patients with COPD. It also shows that insomnia in COPD was associated not only with medical and psychiatric comorbidities but also with increased health care utilization.

While causative factors for insomnia in COPD are many, poor sleep quality as assessed by validated questionnaires such as the Pittsburgh Sleep Quality Index has been consistently shown to be associated with an increased risk of exacerbations (Shorofsky M et al. Chest. 2019:156:852-63). Therefore, frequent nighttime symptom burden coupled with sleep disturbance represents a modifiable risk factor in patients with COPD (Zeidler MR et al. Sleep. 2018;1:41(5);zsy044). Routine evaluation for sleep quality and assessment for factors driving insomnia should be done in patients with COPD. Addressing insomnia in conjunction with sleep-disordered breathing offers the opportunity to improve COPD outcomes.

Short sleep predicts incident dementia and all-cause mortality

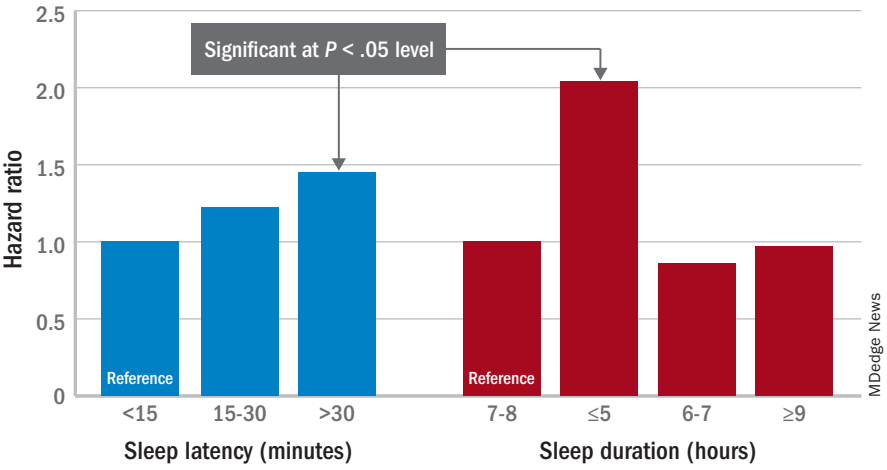
BY HEIDI SPLETE
FROM AGING

More evidence has emerged linking sleep deficiency, dementia, and mortality.

"Sleep disturbance and insufficiency have been shown to be associated with both the development and progression of Alzheimer's disease and with all-cause mortality," wrote Rebecca S. Robbins, PhD, of Brigham and Women's Hospital, Boston, and colleagues. However, research on this topic has yielded conflicting results, and "few studies have included a comprehensive set of sleep characteristics in a single examination of incident dementia and all-cause mortality."

In a study published in Aging (2021 Feb 11;13[3]:3254-68. doi: 10.18632/aging.202591), the researchers identified 2,812 adults aged 65 years and older from the National Health and Aging Trends Study (NHATS), a nationally representative longitudinal study of Medicare beneficiaries aged 65 years and older in the United States.

Association between sleep disturbance and incident dementia



Note: Based on data for 2,812 Medicare beneficiaries included in the 2013 and 2014 National Health and Aging Trends Study surveys.
Source: Aging. 2021 Feb 11;13(3):3254-68. doi: 10.18632/aging.202591

Participants completed surveys about sleep disturbance and duration in 2013 (1,575 individuals) and in 2014 (1,237 individuals), and the researchers examined the relationship between sleep disturbance and deficiency and incident dementia and all-cause mortality over the next 5 years. The average age of the study participants was 76.9 years, 60% were women, and 72% were White.


amenic181/Getty Images

Overall, approximately 60% of the participants reported never or rarely having problems with alertness, approximately half said that they rarely or never napped, and more than half said they fell asleep in 15 minutes or less. Approximately 70% rated their sleep quality as good or very good, and more than 90% said they rarely or never snored.

The researchers examined the relationships between sleep characteristics and the development of incident dementia over 5 years. In a fully adjusted Cox multivariate analysis, individuals who slept 5 hours or less per night had approximately twice the risk for incident dementia as those who slept longer (hazard ratio, 2.04); risk of dementia also was higher among those who took 30 minutes or longer to fall asleep (HR, 1.45).

In addition, the risk of all-cause mortality was significantly higher among individuals who reported difficulty maintaining alertness some days or most days/every day (HR, 1.49 and HR, 1.65, respectively), routinely nap-

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Study links sleep meds and dementia risk in older adults with sleep problems

BY HEIDI SPLETE
FROM SLEEP MEDICINE

Sleep medications for older patients who report sleep problems may not be the best treatment given growing evidence of the link between these medications and the risk of incident dementia.

Adults aged 65 years and older who used sleep medications 5-7 days a week demonstrated a 30% increased risk of dementia, compared with those who did not use sleep medications, findings from a prospective study of 6,373 individuals show.

Adults aged 65 and older report a higher burden of sleep problems than other age groups, but major medical associations discourage the use of sleep medications by older adults because of growing evidence of a link between sleep medication use and cognitive decline, wrote Rebecca Robbins, MD, of Brigham and Women's Hospital, Boston, and colleagues. However, data on this association among adults in the United States are limited, they said.

In a study published in Sleep Medicine, the researchers surveyed 6,373 adults aged 65 years and older who were enrolled in the nationally representative National Health and Aging Trends Study (NHATS). The majority of the participants were non-Hispanic White (71%), 59% were women, and 21% ranged in age from 70 to 74 years.

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ping some days or most days/every day (HR, 1.38 and HR, 1.73, respectively), poor or very poor sleep quality (HR, 1.75), and sleeping 5 hours or less each night (HR, 2.38).

The study findings were limited by several factors including a population representing only one-quarter of the NHATS cohort, which prevented nationally representative estimates, the availability of only 2 years of sleep data, and small sample size for certain response categories, the researchers noted.

However, "our study offers a contribution to the literature on sleep among aging populations in its assessment of incident dementia and all-cause mortality and a range of sleep characteristics among older adults," they said. In particular, "short sleep duration was a strong predictor of both incident dementia and all-cause mortality, suggesting this may be a sleep characteristic that is important – over and above the other predictors – of adverse outcomes among older adults," and future areas for research include the development of novel behavioral interventions to improve sleep in this population.

The study was supported in part by the National Institute for Occupational Safety and Health; the National Heart, Lung, and Blood Institute; the National Institute on Aging; and the Brigham Research Institute Fund to Sustain Research Excellence. Lead author Dr. Robbins disclosed fees from Denihan Hospitality, Rituals Cosmetics, Dagmejan, Asystem, and SleepCycle. Several coauthors disclosed relationships with multiple pharmaceutical companies, and support from various philanthropic organizations.

Commentary by Dr. Benca

Across the life span, individuals reporting less than recommended amounts of sleep are more likely to experience numerous adverse health outcomes, including psychiatric disorders, suicidal behaviors, obesity, cardiovascular disease, cognitive complaints, accidents, and mortality. In older adults, sleep problems including insomnia, reduced total sleep, and prolonged sleep latency have been associated with increased mortality as well as dementia, particularly Alzheimer's disease (AD).

The association of reduced sleep time and AD may be explained by the bidirectional relationship between sleep and AD pathology. In AD, amyloid-beta plaques and tau protein tangles accumulate in the brain, resulting in nerve cell dysfunction and loss. Normally, amyloid and tau proteins are cleared from the brain during sleep, particularly deep slow wave sleep. Disturbed sleep thus interferes with their clearance, and conversely, as these substances build up in the brain they interfere with sleep, setting up a vicious cycle. The association between poor sleep and mortality is likely multifactorial, given the impact of sleep loss and sleep disorders on many medical conditions.

Whereas prior studies have tended to look at the predictive value of sleep problems on either dementia or mortality, this large epidemiological sample of elderly subjects demonstrated that both dementia and mortality were associated with self-reported sleep amounts of less than 5 hours within the same cohort. Interestingly, subjects who reported obtaining 6-7 hours of sleep had lower risks of subsequent dementia and mortality, and this sleep amount is consistent with the recommendation for 6-8 hours of sleep in those aged over 65 years.

A critical question is how much reduced sleep duration is actually contributing to the increased risks of dementia and death, or if instead sleep difficulties are an early sign of neurodegenerative and other physiological processes leading to health problems. Clearly, well-controlled intervention studies are needed to determine whether treating insomnia and other sleep disorders can improve health outcomes in the elderly.

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Participants responded to questions about routine sleep medication use. Routine was defined as "most nights" or "every night." The data were collected for an 8-year period from 2011 to 2018. The study began in 2011, with a core interview administered annually.

Approximately 15% of the study population reported routine use of sleep medications. Overall, routine use of sleep medication was significantly associated with risk of incident dementia (hazard ratio, 1.30; $P < .01$) after controlling for multiple variables including age, sex, education level, and chronic conditions.

Dementia screening was conducted by participants rating their memory and then performing a memory-related activity (immediate and delayed 10-word recall) and other exercises to assess executive function and orientation. A separate eight-item informant screener was performed for patient proxies. The researcher noted, "Sensitivity of the NHATS probable dementia screening measure has been determined in previous research to be 66%, and specificity is 87%, with respect to a clinical dementia diagnosis."

The study findings were limited by several factors including the use of self-reports, the lack of data on type or dose of sleep medication, and lack of data on the indication for the prescription, the researchers noted.

"Also, sleep medication use leads to worse performance on cognitive testing, such as the questionnaires used to screen for dementia in this study, and therefore could have resulted in a false diagnosis of dementia," they added.


Dr. D'Ambrosio

However, the results were strengthened by the large, nationally representative study population and support the need for quality geriatric care, the researchers said.

"Our findings provide further support and evidence that sleep medications are all too commonly administered, yet associated with greater risk for incident dementia, and that the U.S. health care system is in need of creative solutions for addressing poor sleep among older individuals," they concluded.

Implications and alternatives

The study is important as the number of aging Americans increases, said Carolyn M. D'Ambrosio, MD, FCCP, of Brigham and Women's Hospital and Harvard Medical School, Boston, in an interview. "In the elderly, inability to fall asleep or stay asleep are common issues that are brought to a health care provider," she said.

Dr. D'Ambrosio said she was not surprised by the study findings "as elderly patients often have sleep issues and sometimes a well-meaning health care provider gives them sleep medication to help. We have known that some of these sleep medications such as benzodiazepines affect cognitive performance," she said.

Dr. D'Ambrosio said she avoids prescribing sleep medications for older adults if possible. "A deep dive into sleep habits, environment, and other things that disrupt sleep often gets to the problem rather than just masking it with a sleep medication," she noted. Alternatives to improve sleep in older adults include exercise, exposure to bright light during the day, and good healthy sleep habits, all of which contribute to improved sleep in the elderly, said Dr. D'Ambrosio. She also recommends screening older adults for other issues that affect sleep, such as chronic pain.

The current study highlighted the association between sleep medication use and dementia, but it does not show causation, Dr. D'Ambrosio said. "So much more needs to be done to determine whether the sleep medications are causing worsening cognitive function long term,

Commentary by Dr. Sundar

Over the next few decades, it is expected that more than 10 million U.S. adults will be affected with dementia. Besides the morbidity and mortality stemming directly from dementia to the patient, there is also a significant burden on the health care system from the costs of caring for these patients. Among the many factors that may cause Alzheimer's disease (AD), the role of sleep disturbance in leading to amyloid-beta and tau protein accumulation – the basis of neurodegeneration because of neurofibrillary tangle formation – is becoming better recognized (Neuropsychopharmacology. 2020;45:104-20).

Among the multitude of sleep-related disturbances, sleep duration is a key factor in amyloid-beta and tau clearance. While bidirectional relationships between amyloid-beta and tau deposition and sleep have been shown, the finding of sleep medication use for 5-7 days a week being a risk factor for dementia in this large national health and aging trends study adds significantly to the existing literature linking sedative medication use and AD. A key finding is the significant proportion of adults aged more than 65 years that reported routine use of sleep medications (15%), which represents 4.6 million older U.S. adults. Despite adjusting for a variety of demographic and comorbid disease–related risk factors, a significant hazard ratio of 1.3 was noted for incident dementia in routine sleep medication users over an 8-year duration. The authors discuss a number of factors explaining this association, including sleep disruption in preclinical AD. While mechanistic aspects of this relationship need to be elucidated, practitioners need to be cautious with sleep medication use in an elderly population.

or if the dementia is starting but not yet diagnosed and the sleep medication is given but not the cause of the dementia," she noted.

Research gaps and treatment strategies

Older adults experiencing sleep difficulties may try various medications including pharmacologics (for instance, benzodiazepines), over-the-counter agents, such as diphenhydramine or doxylamine preparations, and/or herbal and nutritional supplements such as valerian or melatonin, said Mary Jo S. Farmer, MD, FCCP, of the University of Massachusetts Medical School–Baystate, Springfield, in an interview. "However, sleep medications, particularly benzodiazepines, are strongly discouraged by major medical associations including the American Geriatrics Society in part because of the growing evidence that use of sleep medications is associated with cognitive impairment and decline," she said.

The current study results contribute to previous work demonstrating that both pharmacologic and nonpharmacologic sleep medication, although commonly administered, is associated with subsequent adverse outcomes in older adults, Dr. Farmer said. This association sets the stage for creative and different solutions for addressing poor sleep among older adults, such as behavioral treatments including cognitive-behavioral therapy, she noted.

Dr. Farmer

Dr. Farmer said, "Areas for future research include exploring the causal link between prescription and/or over-the-counter sleep medication use and incident dementia in a randomized controlled trial," she added.

"Another interesting opportunity for future research is to explore the indications for sleep medications among older adults since it has been shown in the general population that sleep difficulties represent only 12% of the indication for sleep medication prescriptions," Dr. Farmer noted. "Future research could examine the strength of the underlying motivation to use sleep medication even in light of suggested long-term effects, and the effectiveness of other measures to avoid or minimize sleep difficulties," she said.

"My experience is that the majority of ambulatory patients recently seen in sleep clinic want to avoid long-term use of sleep medications and will ask what other measures can be tried to consistently achieve a good night's sleep without medication use," Dr. Farmer said. "If medications are used, patients would rather try melatonin than a benzodiazepine. Many patients who come to sleep clinic with sleep medications already prescribed and are subsequently found to have sleep apnea and/or restless legs find that they no longer need sleep medication when these other medical conditions are appropriately diagnosed and managed," she explained. "Finally, many patients tell me they feel less energetic upon awakening, almost feel hung over, and express being less sharp cognitively when taking pharmacologic sleep medication, whether for short or long periods of time, and therefore they want to avoid continuing with sleep medication use," she said.

Dr. Farmer's strategy for developing alternatives to sleep medications in older adults includes taking a careful history, including a complete list of medical problems, review of medications, and a thorough sleep history including usual time of sleep onset, awake time, and the frequency of daytime naps. "Tips for improving the quality of nighttime sleep may include adequately treating pain and other medical conditions such as heartburn, sleep apnea, and restless legs, creating a soothing environment to promote sleep by eliminating noise and bright lights, avoiding stimulant medications and substances such as caffeine and nicotine before bedtime, avoiding excessive amounts of alcohol, avoiding diuretics before bedtime, encouraging physical activity during the day, spending time in the sunlight as much as possible to help regulate the sleep cycle, limiting daytime naps, and establishing a regular sleep schedule," she said.

Gravity Images/The Image Bank/Getty Images

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